The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte STEPHEN DONOVAN

Appeal No. 2005-0193
Application No. 09/371,354

ON BRIEF

MAILED

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U.S. PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

ELLIS, SCHEINER, and GREEN, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 7, 15-17, 37 and 38. Claims 1-6, 8-14, and 18-36 have been canceled.

Claim 7 is representative of the subject matter on appeal and reads as follows:

> 7. A method for treating bradycardia, the method comprising the step of intrapericardial injection of a botulinum toxin to the sinoatrial node or to the atrioventricular node of a heart of a patient with bradycardia, thereby treating bradycardia.

The references relied upon by the examiner and the appellant are:

Tsuboi, Masato et al. (Matsato I),[1] "Botulinum neurotoxin A blocks cholinergic ganglionic neurotransmission in the dog heart," Jpn J Pharmacol, vol. 89(3), pp. 249-254 (2002).

Mangrum et al. (Mangrum), "The evaluation and management of bradycardia," New Eng J Med, vol. 342(10), pp. 703-709 (2000).

Tsuboi, Matsato et al. (Matsato II), "Inotropic, chronotropic, and dromotropic effects mediated via parasympathetic ganglia in the dog heart," Am J Physiol Heart Circ Physiol, vol 279, pp. H1201-H1207 (2000).

Johnson, E., "Clostridial toxins as therapeutic agents: Benefits of nature's most toxic proteins," Annu Rev Microbiol, vol. 53, pp. 551-575 (1999).

Claims 7, 15-17, 37 and 38 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

We have carefully considered the respective positions of the appellant and the examiner and find ourselves in substantial agreement with that of the appellant. Accordingly, we reverse.

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[1] The appellant and the examiner both refer to the Tsuboi et al. publications as Masato. For purposes of consistency, we have done so as well.

Background and Discussion

Bradycardia is a cardiac muscle disorder which is characterized by an abnormally reduced heart rate. Specification, p. 1. According to the appellant:

> Bradycardia may be caused, at least in part, by the release of the neurotransmitter acetylcholine from cholinergic parasympathetic neurons of the heart. A possible physiological mechanism with regard to the present invention may relate to inhibiting the acetylcholine release from cholinergic neurons of the heart by injecting a botulinum toxin in a region containing cholinergic parasympathetic neurons (i.e., the SA node or the AV node). By injecting botulinum toxin into such a region, acetylcholine release may be attenuated. The injection resulting attenuation of acetylcholine release can lead to an increase in heart rate, thereby treating bradycardia of a patient. [Brief, p. 2.]

The specification discloses that there are seven (7) immunologically-distinct serotypes of botulinum toxin; viz., A, B, C1, D, E, F and G. Specification, p. 12, lines 23-26. The different serotypes are said to vary in toxicity and duration of the paralysis which they invoke. Id., sentence bridging pp. 12-13. Botulinum toxin type A is said to be the most potent of the seven known serotypes. Id., p. 13, lines 1-2.

As indicated by claim 7, above, the present invention is directed to a method of treating bradycardia which comprises injecting botulinum toxin into the sinoatrial (SA) node or the atrioventricular (AV) node of a patient's heart.

The examiner contends that the specification is prophetic in its disclosure of a method of treating bradycardia using botulinum toxin. Answer, p. 4. The examiner argues that the specification does not disclose (i) any methods or working examples with respect to the administration of botulinum toxin to cardiac muscle or cells; (ii) the time period in which the toxin should be administered or for how long; (iii) any side

time period in which the toxin should be administered or for how long; (iii) any side effects that are experienced by the patient following administration of botulinum toxin; and (iv) the specific dosage of botulinum toxin to administer. Id., pp. 4-5. The examiner contends that it would require undue experimentation for one skilled in the art to determine the optimal dose of botulinum toxin to be administered without damaging a patient's heart. Id., p. 5. The examiner points out that there are many complications associated with botulinum therapy. Id. The examiner relies on Johnson for support. In addition, the examiner argues that the present invention is unpredictable and complex. Id., p. 6. Thus, the examiner concludes that

> Due to the large quantity of experimentation necessary to treat bradycardia by administering any botulinum toxin to the SA node or AV node of the heart and to determine the dosage and safety of botulinum toxin and the timing and duration of administration without irreversible injury or actually killing the patient, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art . . . and the unpredictability of the effects of any botulinum toxin on a subject, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. Id.

It is well established that the examiner may reject the claims as being based on a non-enabling disclosure when s/he has reason to conclude that one skilled in the art would be unable to carry out the claimed invention. Fiers v. Revel, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993); In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). However, "a specification disclosure which contains a

teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." In re Marzocchi, 439 F.2d at 223, 169 USPQ at 369.

Here, we appreciate the examiner's concerns with respect to the enablement issue, however, a determination of whether undue experimentation is required to "make and use" the claimed invention is reached after weighing many factual considerations. In addition, we point out that a prima facie case of non-enablement can be rebutted, as it has been in this case. Here, we find that the appellant has provided rebuttal evidence in the form of three (3) declarations and the Masato I publication. Thus, even though the examples are all prophetic, the appellant has submitted evidence that the specification provides an enabling disclosure. See, Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (CCPA 1984)("Use of prophetic examples, however, does not automatically make a patent non-enabling").

First, we find that two highly-qualified experts, Dr. Longhurst, a cardiologist (head of the Department of Cardiology at the University of California, Irvine) and Dr. Brin,[2] a physician and, currently, Vice President, Botox®/Neurology at Allergan, Inc.,[3] state that given the teachings of the specification, one skilled in the art would have been able to treat bradycardia by intrapericardial injection of botulinum toxin to a patient's heart.

Second, with respect to the dosage issues raised by the examiner, we find Dr. Longhurst's statement (Longhurst Declaration I, para. 7) that "the specific dosage of the botulinum toxin to use entail consideration of factors such as the patient's size, weight, age, and disease severity which factors are routine considerations determined on a patient to patient basis by a cardiologist of ordinary skill who has knowledge of the therapeutic use of botulinum toxin," to be reasonable. Moreover, as acknowledged by the examiner, the dosages set forth in the claims overlap those used to treat the bradycardia animal (canine) model[4] taught by Masato I. Thus, we find the examiner's

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[2] Dr. Brin states that he "was one of the first investigators to examine the use of botulinum toxin for the treatment of medical disorders" and that he "pioneered the use of botulinum toxin for the treatment of dystonias, including blepharospasm and other debilitating neurological disorders." Declaration, para. 5.

[3] Dr. Brin states that as Vice President, Botox®/Neurology at Allergan, Inc., he oversees the Botox® (botulinum toxin type A purified neurotoxin complex) development portfolio, and directs clinical programs for uses of the botulinum toxins. Declaration, para. 12.

[4] Masato uses dogs, wherein reduced heart rate is induced by stimulation of the preganglionic parasympathetic nerves using electrical stimulation, as an animal model of human bradycardia.

criticism that it would require undue experimentation to determine the appropriate dosage to be unsupported by the evidence of record.

Third, we find appellant's reliance on the Masato I publication to be appropriate and informative. We point out that the appellant can rely on a later-dated publication as evidence of the level of ordinary skill in the art at the time of the application and as evidence that the disclosed method would have been operative. Gould v. Quigg, 822 F.2d 1074, 1078-79, 3 USPQ2d 1302, 1305 (Fed. Cir. 1897). In this case, we find that the examiner does not challenge the dog as being the appropriate animal model of bradycardia. Rather, the examiner argues that the canine model is "not predictive of the scope of the claims" because Masato I (i) use electrically-stimulated preganglionic parasympathetic nerves to induce bradycardia which "may" be different from normally-induced bradycardia; and (ii) inject botulinum toxin A into the SA fat pad rather than the SA node or the AV node. Answer, p. 9. We find these arguments to be unpersuasive for the reasons set forth in the appellant's reply brief.

Briefly summarized, we agree with the appellant that what is critical is that the electrical stimulation employed by Masato I stimulates the same population of nerve cells that are involved in bradycardia conditions. It is immaterial how said nerve cells are stimulated, rather, it is the type of nerve cells (preganglionic parasympathetic) and the condition induced (bradycardia) which are important. Moreover, as pointed out by the appellant, electrical stimulation is well-established in the scientific community as a

method which the researcher can control and more readily evaluate the experimental results.

With respect to the administration of botulinum A toxin to the fat pads, we find the appellant's explanation that both the SA fat pad and the SA node contain a high proportion of cholinergic parasympathetic neurons and that the administration of the toxin to the fat pads is sufficient to confirm the operability of the administration of the toxin to said neurons of the heart, to be reasonable and convincing. Brief, p. 22.

As to the fact that Masato I only discloses the use of botulinum toxin A, we find the appellant's response that the determination of the dosage of the various types of botulinum toxin is routine procedure for a physician to be both reasonable and supported by the evidence of record. Reply Brief, pp. 4-5; Longhurst declaration I, para. 7.

Finally, we recognize that the examiner applied the factors set forth by our appellate reviewing court in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), in making his determination that the specification fails to provide an enabling disclosure of the claimed invention. However, we find the appellant's application of said factors more accurately reflects the facts of this case. Rather than burden the record with unnecessary repetition, we direct attention to pages 14-23 of the appellant's main brief.

In view of the foregoing, the decision of the examiner is reversed.

REVERSED

Joan Ellis
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Lora M. Green
Administrative Patent Judge

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JE/eld

Frank J. Uxa
Stout, Uxa, Buyan &Mullins, LLP
4 Venture, Suite 300
Irvine, CA 92618